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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/991,721 | 11/13/2001 | J. Andrea McCart | NIH174.001C1 | 5587 |

45311 7590 06/28/2006

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| EXAMINER | |
|---|---|
| SULLIVAN, DANIEL M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/991,721 | MCCART ET AL. | |
| | Examiner | Art Unit | |
| | Daniel M. Sullivan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13,15,17,18,25 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,17,18,25 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is reply to the Paper filed 8 May 2006 in response to the Final Office Action mailed 3 February 2006. Claims 1-13, 15, 17, 18, 25 and 45-50 were considered in the 3 February Office Action. No amendments were filed with the 8 May Paper. Claims 1-13, 15, 17, 18, 25 and 45-50 are pending and under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

### *Response to Arguments and the Declaration under 37 CFR §1.132*

Claim Rejections - 35 USC § 103

Claims 1-12, 15, 17, 25, 45-48 and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* (1995) WO 95/31105 in view of Dorner *et al.* U.S. Patent No. 6,103,244 and in view of Buller *et al.* (1988) *J. Virol.* 62:866-874 for the reasons of record and herein below in the response to arguments and the Rule 1.132 Declaration.

Claims 1 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claim 1 above, and further in view of Zhang *et al.* (1996) *Biochem. Biophys. Res. Commun.* 227:707-711

for the reasons of record and herein below in the response to arguments and the Rule 1.132 Declaration.

Claims 1, 12 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claims 1 and 12 above and further in view of Paoletti U.S. Patent No. 5,942,235 for the reasons of record and herein below in the response to arguments and the Rule 1.132 Declaration

Claims 1, 12 and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* and further in view of Paoletti (*supra*) as evidenced by UniProtKB/Swiss-Prot Database entry P04637, P53_HUMAN (hereinafter, P04637) for the reasons of record and herein below in the response to arguments and the Rule 1.132 Declaration.

*Response to Arguments and the Declaration under 37 CFR §1.132*

In response to the *prima facie* rejections and arguments of record, Applicant has submitted a Declaration under Rule 1.132 by two of the named inventors and asserts that the statements and showings contained therein demonstrate that the prior art failed to provide the suggestion to combine references and that the declaration demonstrates synergism, which evidences nonobviousness.

Applicant's arguments and the Declaration have been fully considered but are not deemed persuasive. Regarding establishing nonobviousness by a showing of synergism, MPEP 716.02(a) states:

> Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.).

Thus, synergism alone is not sufficient to establish nonobviousness if the results are not greater than what would have been expected.

In paragraph 3, the Declaration states that the double deletion mutant (vvDD) yielded reduced viral production compared to wild-type (WT), TK-, or VGF- viruses from resting cultures of NIH3T3 cells but equivalent production from dividing cultures (results are shown in Figure 1 of the application) and cites an experiment (presented in Figure 5 of the application) showing virus production in brain and tumor of nude mice after i.p. injection with WT, TK-, VGF- and vvDD. However, it is not clear from the data presented that the effect of the double deletion is truly synergistic. As shown in Figure 1 of the specification, viral recovery from 3T3 cells infected with vvDD is essentially the same as viral recovery from VGF- and TK- cells in both resting and dividing cultures. Although Figure 5 does show that production of vvDD virus

in the brain of nude mice is less than production of either the VGF- or TK- virus, it is not clear that this reduction is greater than the sum of the effect of each mutation taken separately. In fact, it would appear from the Figure that the effect of each individual mutation is much greater than the additional effect of the combined mutation (it is noted that Figure 5 presents the data on a log scale). Specifically, it appears that the wild type virus produced approximately 12,000 pfu/mg protein in brain while each of the VGF- and TK- viruses produced approximately 100 pfu/mg protein in brain (a 99% reduction in virus production). The result of the combined mutation was to eliminate the remaining 1% of virus production in brain. On the other hand neither the VGF- mutation nor the TK- mutation had a significant effect on virus production in tumor cells and the combined mutation similarly had no significant effect. In sum, the data indicate that the combined mutation provided a 1% reduction in virus production in brain beyond the reduction obtained with either mutation alone while providing the same amount of virus production from tumor cells.

The Declaration also cites Figure 6 of the application as demonstrating significant tumor regression in nude mice bearing s.c. colon adenocarcinoma. However, as the Figure does not present any data for VGF- or TK- viruses, it is not possible to determine whether the results obtained with the vvDD virus are synergistically better than results obtained using viruses containing mutations of either of the VGF or TK genes alone.

Therefore, viewed as a whole, the data presented in the declaration do not demonstrate a combined effect on tumor selectivity that is synergistic. Furthermore, even if one were to accept, *arguendo*, that the additional reduction in virus production in brain tissue of nude mouse was synergistic effect, as pointed out in the previous Office Action, McCart *et al.* teach, based on

consideration of what was known in the prior art, that the combined effect of TK and VGF deletions should be synergistic.

Regarding the statement of McCart *et al.* cited in the previous Office Action (i.e., "The combined effect of TK and VGF deletions on tumor specificity should be synergistic"), Declarants contend that the statement does not negative patentability. In paragraph 14, Declarants contend that the statement was written in hindsight and could not be predicted based on the two deletions separately. In paragraph 15, Declarants state that one would not infer from the NYVAC.2 literature that the combination of the two mutations (TK and VGF) were sufficient for obtaining the effects sought and that the combination may have restored over attenuation as in NYVAC.2. Declarants contend that there was nothing in the literature to suggest a mutant vaccinia virus with multiple selective mutations to enhance tumor specificity.

These statements have been fully considered but are not deemed persuasive. The passage from McCart *et al.* at issue reads in full:

> Previously, deletion of either the TK gene or VGF genes was shown to significantly decrease pathogenicity compared with WT virus [Buller *et al.* (1985) *Nature* 317:813, Buller *et al.* (1988) *J. Virol.* 62:866-874]. A TK- virus requires TTP for DNA synthesis from the nucleotide pool present in dividing cells. This leads to preferential viral replication in dividing cells and is the presumed explanation for the observed tumor specificity. We have shown previously that a systemically delivered TK- vaccinia virus expressing the firefly luciferase gene resulted in up to 3 logs higher gene expression in murine tumors compared with normal tissues [McCart (2000) *Gene Ther.* 7:1217, Puhlmann *et al.* (2000) *Cancer Gene Ther.* 7:66, Gnant *et al.* (1999) *Ann. Surg.* 230:352]. Further improvement in both tumor specificity and safety of vaccinia is required before its use as a systemic gene therapy vector in humans.
>
> VGF is a secreted protein produced early in viral infection and acts as a mitogen to prime surrounding cells for vaccinia infection [Buller *et al.* (1988) *Virol.* 164:182]. Deletion of this growth factor causes decreased viral replication in resting cells and a 1000-fold increase in the LD50 of intracranial vaccinia [Buller *et al.* (1988) 62:866]. The combined effect of TK and VGF deletions on tumor specificity should be synergistic. In the absence of TK, viral replication will require TTP from dividing cells. The normal stimulation of surrounding cells to divide will not occur in the absence of VGF; hence, replication will occur only in actively dividing cells. As well as decreasing pathogenicity, this is expected

to maintain or enhance the tumor selectivity reported previously [McCart (2000) *Gene Ther.* 7:1217, Puhlmann *et al.* (2000) *Cancer Gene Ther.* 7:66, Gnant *et al.* (1999) *Ann. Surg.* 230:352].

Viewed as a whole, the conclusion that the combined effect of TK and VGF deletions on tumor specificity should be synergistic expressed in McCart *et al.* is clearly reasoned from a consideration of knowledge available to one of ordinary skill in the art at the time the instant application was made. In contrast to Declarant's contention that there was nothing in the literature to suggest a mutant vaccinia virus with multiple selective mutations to enhance tumor specificity, McCart *et al.* cites several prefiling publications to support the conclusion that the combination of a TK deletion and a VGF deletion would provide enhanced tumor selectivity.

With regard to the NYVAC.2 literature, it is first noted that the art cited in the rejections as teaching the mutant vectors do not teach NYVAC.2 (they teach single deletions comprised within a WR strain) and, as Declarant points out in paragraph 11, the NYVAC.2 comprises more than 40 ORF deletions in addition to the TK and VGF deletions. In view of the extensive additional modifications comprised by the NYVAC.2 strain, the skilled artisan would not have considered the over attenuation exhibited thereby as suggesting that similar over attenuation would result from combining a TK deletion with a VGF deletion in a WR strain as suggested by the prior art. Furthermore, in view of the prior art discussed by McCart *et al.*, the skilled artisan would not have considered improved tumor specificity of the degree demonstrated in the application to be unexpected.

In paragraph 15, Declarant cites other statements which are asserted to indicate that a complete explanation for tumor selectivity shown by the current vector has yet to be elucidated and asserted to acknowledge that the preliminary explanation is hypothetical.

The passages cited by Applicant read as follows:

> The most important feature of this virus, however, is the ability to selectively replicate and express genes in tumor tissues compared with normal tissues. We have demonstrated previously a 3-log higher expression of luciferase in tumors compared with normal tissue in a s.c. tumor model after systemic administration of the virus (7). The complete explanation for this tumor selectivity has yet to be elucidated; however contributing factors include the enhanced ability of macromolecules to extravasate through permeable tumor vasculature (49) and the replication selectivity shown by vaccinia within the preferred metabolically active environment of tumor cells. Evidence for the contribution of permeable vasculature comes from smallpox literature. Smallpox was known to replicate preferentially in areas of increased vascular permeability secondary to injury and histamine release (50). The biodistribution of vaccinia (7, 35, 36), predominantly to tumor and ovarian follicles (both sites of increased vascular permeability; Refs. 49, 51), is also suggestive. Recently, we have shown that hyperthermia, which increases vascular permeability, leads to increased uptake of vaccinia virus. Of interest, ovaries have been shown to have high levels of VEGF (which also increases vascular permeability) and may explain the propensity for the virus to localize there as well as in tumor (52). Tumor-selective replication has been demonstrated previously (7, 53) and is thought to be largely attributable to the rapid division of tumor cells that provide nucleotides, specifically TTP, to complement a TK-deleted vector. The hypothesis for the high level of tumor selectivity shown by the current vector is a combination of the two. vvDD-GFP travels intravascularly and escapes at sites of increased vascular permeability, such as the tumor and ovary. Because of its ultimate reliance on dividing cells for replication, it is only able to replicate efficiently within tumor cells or ovarian follicles. Other sites of cellular replication such as bone marrow and gastrointestinal mucosa do not demonstrate the same levels of vaccinia infection, possibly because of a lack of leaky vasculature.

The statement regarding the tumor selectivity cited by Declarants appears to be referring to selectivity of vaccinia virus in general and not specifically the vvDD virus. Furthermore, the combination referred to in the "hypothesis for the high level of tumor selectivity" is the combination of increased vascular permeability in tumor beds and the ultimate reliance on dividing cells for replication. The passage clearly does not suggest that the effect of combining a TK deletion with a VGF deletion would not be expected to enhance tumor selectivity and does not undermine the analysis presented in the introduction of McCart *et al.* or the conclusion that the combined effect of TK and VGF deletions on tumor specificity should be synergistic.

In paragraph 11 of the Declaration, Declarants contend that the prior art lacks any suggestion that the references should be combined in a manner required to meet the claims. Declarants contend that nothing in the prior art suggested the desirability of combining the TK and VGF deletions because no additive effect might have been achieved and the combination might have restored over attenuation as in NYVAC.2.

This argument has been fully considered but is not deemed persuasive. As stated in the Office Action mailed 12 May 2005 (p. 6, ¶2), "One would be motivated to combine these teachings based on the nature of the problem to be solved by the teachings of Mastrangelo *et al.*, which is to deliver immune active cytokines into tumor cells by means of a vaccinia virus vector, statements made in Dormer *et al.* indicating that the vector disclosed therein [which comprises a TK- mutation] is particularly advantageous because it enables direct cloning of genes into the vector [], the teachings of Dormer *et al.* indicating that it is desirable to use vector strains comprising mutations of genes that result in decreased virulence [] and the teaching of Buller *et al.* that the VGF- mutation might be a desirable attenuation marker for inclusion in vaccine vectors []." Dormer *et al.* explicitly teaches a vector comprising a TK- mutation, teaches that, in the interest of safety, it is desirable to attenuate the vector and cites the VGF gene as among those that have been shown to decrease virulence of vaccinia strains (see especially bridging col. 3-4 of Dormer *et al.*; cited at page 5, ¶2 of the 12 May Office Action). With regard to the possibility that no additive effect might be achieved, Applicant is reminded that obviousness requires only a reasonable expectation of success. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. Obviousness does not require absolute predictability. See MPEP 2143.02. As stated in making

the *prima facie* rejection, "Dorner *et al.* demonstrates that the TK⁻ vector described therein is an efficacious delivery vehicle and Buller *et al.* found that deletion of the VVGF gene, in spite of its effect of reducing virulence of the virus *in vivo*, did not affect virus replication under optimal cell growth conditions *in vitro* (see especially the paragraph bridging pages 871-872). Thus, one would have a reasonable expectation of success in combining the TK⁻ and VVGF⁻ phenotypes in a single vector for use in the method of Mastrangelo *et al.*" (12 May Office Action bridging p. 6-7).

With regard to the possibility of over attenuation, it is noted that tumor selectivity is not relied upon for motivation to combine the references. Instead, the motivation to combine the references comes from teachings in the art that it is preferable to use vaccinia vectors having reduced virulence and that deletion of the VGF and TK genes produces vectors having reduced virulence. "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." (MPEP 2144.) Thus, even if one were to expect, *arguendo*, that combining VGF and TK genes would result in a vector that is "over attenuated" with respect to tumor selectivity, that possibility would not dissuade the skilled artisan from combining the teachings as suggested in the art. Furthermore, even if the possibility of over attenuation were relevant to the question of motivation, as stated above, in view of the extensive additional modifications comprised by the NYVAC.2 strain, the skilled artisan would not have considered the over attenuation exhibited thereby as suggesting that similar over attenuation would result from combining a TK deletion with a VGF deletion in a WR strain as suggested by the prior art.

Finally, in paragraph 12, Declarants assert that the invention utilizes a new principle of operation. However, in applying prior art under 35 USC §103, a "principle of operation" is relevant only to the extent that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. (See MPEP 2143.01). The discovery of a new principle of operation does not distinguish a claimed product from the prior art if the product itself would be obvious in view of the teachings of the prior art because the principle of operation is inherent to the product.

Applicant's arguments and the Declaration 37 CFR §1.132 have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §103(a) as obvious over the art.

***Conclusion***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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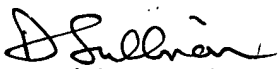

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636